PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	See form PCT/ISA/210
Applicant's or agent's file reference: 03705pct	FOR FURTHER ACTION: See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/001371	11.02.2005	13.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07K16/18

Applicant
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1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/001371

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/001371

Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	7-13, 15-35	YES
	Claims	1-6, 14	NO
Inventive step (IS)	Claims	22, 23	YES
	Claims	1-21, 24-35	NO
Industrial applicability (IA)	Claims	1-35	YES
	Claims		NO

2. Citations and explanations:

1. Reference is made to the following documents:

D1: LAW AMANDA J ET AL: "The distribution and morphology of prefrontal cortex pyramidal neurons identified using anti-neurofilament antibodies SMI32, N200 and FNP7. Normative data and a comparison in subjects with schizophrenia, bipolar disorder or major depression." JOURNAL OF PSYCHIATRIC RESEARCH. 2003 NOV-DEC, vol. 37, 6, November 2003 (2003-11), pages 487-499, XP002348495 ISSN: 0022-3956

D2: BERNSTEIN H G ET AL: "Increased number of nitric oxide synthase immunoreactive Purkinje cells and dentate nucleus neurons in schizophrenia." JOURNAL OF NEUROCYTOLOGY. AUG 2001, vol. 30, 8, August 2001 (2001-8), pages 661-670, XP002348496 ISSN: 0300-4864

D3: HONER W G ET AL: "MONOCLONAL ANTIBODIES TO STUDY THE BRAIN IN SCHIZOPHRENIA" BRAIN RESEARCH, vol. 500, 1-2, 1989, pages 379-383, XP002348497 ISSN: 0006-8993

D4: SIGURDSSON EINAR M ET AL: "Anti-prion antibodies for prophylaxis following prion exposure in mice" NEUROSCIENCE LETTERS, LIMERICK, IE, vol. 336, 3, 23 January 2003 (2003-01-23), pages 185-187, XP002275536 ISSN: 0304-3940

D5: KORTH C ET AL: "MONOCLONAL ANTIBODIES SPECIFIC FOR THE NATIVE, DISEASE-ASSOCIATED ISOFORM OF THE PRION

PROTEIN" METHODS IN ENZYMOLOGY, ACADEMIC PRESS INC, SAN DIEGO, CA, US, vol. 309, 1999, pages 106-122, XP001104847 ISSN: 0076-6879

2. The present application relates to antibodies for the diagnosis and treatment of neuropsychiatric disorders, especially of schizophrenia, depression or bipolar affective disorders.
The advance compared to the prior art is the provision of the two monoclonal antibodies "7B2" and "9C9", which appear to be suitable for the recognition of markers for neuropsychiatric disorders in brain homogenates.

3. Novelty (PCT Article 33(2))

3.1. D1 (Law et al., 2003) compares thin sections from brains of patients with schizophrenia, depression and bipolar affective disorders, and also normal controls. Three monoclonal antibodies against neurofilaments were used, with which immunofluorescence microscopy investigations were carried out. With the antibody N200, which is directed against the "neurofilament 200 protein" (NFH) and is commercially available (Sigma N-0142), a lower detectability of N200-positive neurons was found in samples of patients with depression than in those with schizophrenia or bipolar affective disorders. A trend to increased density of N200-positive neurons was found in schizophrenics compared to the normal controls (page 494, left-hand column, paragraph 2). This antibody would accordingly be suitable for the diagnosis of neuropsychiatric disorders, and thus falls under the scope of protection of claims 1-5 and 14.

3.2. In D2 (Bernstein et al., 2001), immune stains of brain sections of schizophrenic or depressive patients are

compared with normal controls. With a commercially available polyclonal antiserum against a brain-specific isoform of the nitrogen oxide synthase (NOS) enzyme, significantly higher signals were found in the schizophrenic samples than in the two others (cf. page 667, figures 12 and 13). Accordingly, these polyclonal antibodies would be suitable for the diagnosis of schizophrenia and would fall under the scope of protection of claims 1, 2 and 5.

3.3. D3 (Honer et al., 1989) describes the preparation of monoclonal antibodies "to study the brain in schizophrenia" (title). For the immunization of the mice, homogenates of brain samples of schizophrenic patients were used. D3 is therefore considered to be prejudicial to the novelty of claims 1, 2, 5, 6, and 14.

3.4. In summary, it can be stated that claims 1-6 and 14 do not meet the requirements of **PCT Article 33(2)** since their subject matter is not novel.

4. Inventive step (PCT Article 33(3))

4.1. Claims 7-13, 15-21 and 24-35 dependent on claim 1 at present cannot be considered to be inventive under **PCT Article 33(3)**. The claims do not contain any further technical features which, taken alone, would make a contribution to the state of the art, or which would lead to an unexpected effect.

4.2. Claims 22 and 23, which provide the two monoclonal antibodies 7B2 and 9C9, in contrast, do meet the requirements of **PCT Article 33(3)**. The problem addressed by the present invention can be considered that of providing alternative antibodies which are suitable for

Box No. V — Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

the diagnosis of neuropsychiatric disorders. The solution to this problem consists in the specific monoclonal antibodies 7B2 and 9C9.

4.3. Since the prior art already describes antibodies which are suitable for the diagnosis of neuropsychiatric disorders, the concept underlying the invention is not novel. There will be no objection under **PCT Rule 13** (unity of the invention) in this phase. However, it is pointed out to the applicant that this objection might arise on entry into the regional phase administered by the EPO.

Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Clarity

5.1. Claims 1-21 and 24-35 do not meet the requirements of **PCT Article 6** because the subject matter for which protection is sought is not clearly defined. The claims attempt to define the subject matter in terms of the result to be achieved, specifically the recognition of incorrectly folded proteins which are attributable specifically to one disorder.

5.2. In the present case, such a formulation is not, however, admissible, since it is possible to describe the subject matter of the application in more specific terms. An antibody is a protein and must therefore be considered as a chemical substance which should be defined in a claim clearly by reference to technical features, for example to a sequence or to the corresponding hybridoma, and not by the mere statement of its function or by the result to be achieved.

There is no basis whatsoever in the description for the claim that the antibodies described recognize "incorrectly folded" proteins. The idea which supports this concept is apparently derived from the field of prions, for which such antibodies have already been described (see D4 and D5). In the current prior art, there are, however, no indications that incorrect folding of proteins plays a role in the neuropsychiatric disorders mentioned. The Western blots in the application show comparisons between brain homogenates of normal patients, schizophrenic patients and patients suffering from bipolar affective disorder with those of normal patients. Immunoreactive bands which can be

Box No. VIII Certain observations on the international application

attributed specifically to one disorder are marked and the estimated molecular weight is specified, but no statement is made with regard to the identity of these proteins. According to **PCT Article 5**, the invention must be disclosed sufficiently clearly and fully in the description that a person skilled in the art can perform it. The claims must specify the subject matter for which protection is sought and be supported by the description (**PCT Article 6**).

5.3. According to **PCT Rule 5.1(a)(ii)**, the relevant prior art must be specified in the description. This is not done adequately in the present application.